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FDA's Ongoing Efforts to Ensure the Safety, Effectiveness, and Availability of Influenza and Other Vaccines

Statement of

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Introduction

Mr. Chairman and members of the Committee, I am Dr. Lester M. Crawford, D.V.M., Ph.D., Acting Commissioner of the Food and Drug Administration (FDA or the Agency). As you know, the FDA is responsible for the regulation and oversight of vaccines in the United States. I want to assure the Committee, and the public who are here today, that FDA takes their concerns about vaccine safety and availability very seriously. I welcome this opportunity to describe FDA's ongoing efforts to ensure the safety, effectiveness, and availability of influenza and other vaccines licensed in the U.S.

Vaccine Safety

Vaccines have contributed greatly to the health and well being of the people of our nation; however, we must nonetheless be vigilant of any potential safety concern related to vaccines. I will briefly describe some of FDA's vaccine safety activities. In the pre-licensure phase, FDA monitors the safety of investigational vaccines as they are studied in clinical trials conducted under investigational new drug applications. When a manufacturer submits a license application to FDA, we review extensive information describing the manufacture and characterization of the vaccine, the safety and efficacy data from the clinical trials, and we typically inspect the manufacturing facility where the vaccine will be made. In addition, we usually seek advice from our Vaccines and Related Biological Products Advisory Committee on the safety and effectiveness of vaccine candidates. If we determine that a vaccine is safe, effective, and that quality and

consistency of manufacture have been demonstrated, we will license the vaccine.

Post-licensure, we typically review the manufacturer's test results before the manufacturer can release new lots of vaccine to the market. We also inspect the manufacturing facilities every two years. In addition, FDA's Center for Biologics Evaluation and Research (CBER) and the Centers for Disease Control and Prevention (CDC) jointly manage the Vaccine Adverse Event Reporting System (VAERS), a cooperative program for vaccine safety. VAERS is a post-marketing safety surveillance program, collecting information about adverse events (side effects) that occur after the administration of U.S. licensed vaccines. Reports to the VAERS program are welcome from all concerned individuals: patients, parents, health care providers, pharmacists, and vaccine manufacturers. We review these reports on an ongoing basis and obtain additional information as needed.

Influenza Vaccines

To increase our control of this very important disease, efforts are ongoing to increase the availability of influenza vaccine and increase coverage, especially of those individuals at increased risk of complications from influenza. Influenza vaccine is unique among vaccines in that its active ingredients change almost every year and thus presents new manufacturing challenges on an annual basis. Influenza viruses are continuously evolving or mutating, and the

recommendations of which viruses to include in the vaccine each year are based on the surveillance data provided from laboratories worldwide. Early each year, public health experts evaluate the data to determine the strains of virus to be used in the manufacture of the influenza virus vaccine that will be administered in the fall. Currently, licensed vaccines contain three virus strains representing the strains predicted to be in U.S. circulation, as recommended by the U.S. Public Health Service (PHS) [including FDA, CDC, National Institutes of Health (NIH), and National Vaccine Program] for incorporation into the vaccine for 2004-2005. Because of the necessity to have a vaccine that matches the virus strains currently in circulation, vaccines manufactured for the previous year cannot be used.

FDA works closely to facilitate the rapid production of influenza vaccine each year. As soon as the strains are recommended, manufacturers begin to grow the virus strains in fertile hen's eggs. These strains of vaccine, known as "seed strains," used by each manufacturer are tested by FDA's CBER to assure they are the same as the recommended strains. FDA and manufacturers conduct tests to assure the safety and efficacy of the vaccine. Manufacturers submit the results of their testing along with sample vials from each lot to CBER for our "lot release." Because of the complexity of the manufacturing process, CBER performs "lot release" on each lot of influenza vaccine manufactured prior to distribution of the product. "Lot release" consists of CBER's review of the

manufacturers' test results, including tests on the lots of monovalent virus strains. Furthermore, to assure the safety and efficacy of these products, CBER performs additional testing as appropriate.

Although the manufacturing process and lot release is completed for some lots of influenza vaccine as early as July, the manufacturing of additional lots continues until September-October in order to manufacture and complete the testing on a very large number of vaccine doses. There has been a very significant increase in production over the past decade, as compared with approximately 20 million doses per year distributed in the mid-1980s. Because of the fragile infrastructure and decision of manufacturers to leave the market, the burden of production capacity and supply of influenza vaccine rested with thee manufacturers for the 2004-05 flu season. Chiron Corporation (Evans Vaccines Ltd.) manufactures Fluvirin, and Aventis Pasteur, Inc. manufactures Fluzone; both of these vaccines are inactivated influenza vaccines. MedImmune, Inc. manufactures FluMist, a live attenuated influenza vaccine.

2004-05 Flu Season

The loss of Chiron influenza vaccine supply remains a challenge. As you know, we are working hard to assure the safety and health of Americans as the flu season approaches. In coordination with other elements of the Department of

Health and Human Services (HHS or the Department), we have been actively exploring all viable options to secure additional dosages of flu vaccine licensed for use in the U.S. that will provide more Americans protection against the flu. As a result of these efforts, I can report that we have been able to increase the available supply of flu vaccines for the U.S. population to 61 million doses for this flu season.

Coupled with that initiative, we have been contacting manufacturers worldwide in an effort to identify increased supplies of antiviral medications that will provide further protection and treatment for Americans during this flu season and are making progress in this area as well. In addition, we have already been working with our partners in the United Kingdom as well as with Chiron Corporation to complete our review of the problems encountered at their production facility in order to expeditiously determine what steps would be required to bring that facility into compliance.

As a matter of enforcement policy, FDA inspects U.S. licensed vaccine manufacturing facilities every two years. Based on this schedule, FDA inspected the Liverpool, U.K. facility where the Chiron vaccine is produced in 1999, 2001, and 2003. It should be noted that Chiron acquired the facility in July 2003 after FDA conducted the biennial inspection. During the 1999 inspection, FDA identified various concerns and, as a result, issued a warning letter regarding the Liverpool facility. The most significant issues identified in 1999

inspection were the lack of validation for its manufacturing processes, including establishing proper limits for bioburden (including bacteria) and issues related to assuring sterility in the manufacturing process. During the 2001 and 2003 inspections, although FDA found that the company made improvements, we also made observations related to current Good Manufacturing Practices (cGMPs). In each case, FDA reviewed the corrective measures and plans in response to these deficiencies. If fully implemented, the company's plans appeared adequate to correct deficiencies identified at the facility.

It is important to understand that, from the start of the manufacturing cycle, influenza vaccine manufacturing is not a sterile process because it involves the use of eggs, which are not sterile. Therefore, a certain amount of bioburden will be present in early stages of manufacturing. However, vaccine manufacturers must have effective measures, such as sterile filtration, to eliminate this bioburden. As a further safeguard, FDA requires a lot release and testing system for vaccines. This is a vital component of the multi-step safety assurance process for vaccines. It is also important to understand that new flu vaccine is formulated and produced for each flu season, so that concerns identified with vaccine from the prior year's supply do not necessarily relate to the current year's vaccine supply.

FDA's 2004 Communications with Chiron and MHRA

On August 25, 2004, Chiron informed FDA that the company had discovered bacterial contamination in eight lots of final vaccine product for this year's flu season supply and advised that they were investigating the problem. They shared with FDA an overview of their planned investigation to determine root causes of the problem as well as their plan to retest all other lots produced. Chiron quarantined all influenza vaccine lots during its investigation, including those that had passed all required testing, and did not release any of the product.

In September 2004, FDA, CDC and Chiron scheduled weekly conference calls to discuss the status of the firm's investigation. Chiron stated to FDA that the company had identified the cause of the contamination and that the contamination was confined to the identified vaccine lots. The company indicated to FDA that it believed the cause of contamination in these lots could be traced back to one of two contaminated bulk lots used to formulate these final lots. Nonetheless, FDA concurred with the need for Chiron to thoroughly retest all final lots, complete a thorough investigation of the manufacturing process and provide a complete investigation report to FDA. While the investigation was ongoing, Chiron informed FDA that results of the retesting were negative and that the company would submit its final investigative report to FDA during the week of October 4-8.

In late September, Chiron advised that it would substantially meet its plans to supply influenza vaccine to the U.S. On September 28, Chiron's CEO affirmed this in testimony to the Senate Special Committee on Aging when he stated: "As of September 27th, it remains Chiron's expectation that between 46 million and 48 million Fluvirin doses will be delivered to the U.S. market beginning in early October as compared to the 50 million doses projected in July."

MHRA's October 5, 2004 Announcement

On the morning of October 5, 2004, MHRA announced a three-month suspension of Chiron's license to manufacture influenza vaccine. FDA had no prior knowledge of the MHRA's intention to suspend the firm's U.K. license. MHRA's Chief Executive, Professor Kent Woods, indicated that MHRA did not have the legal authority to notify FDA about the suspension announced on October 5 until after MHRA instituted its administrative action. Dr. Woods has also stated that, "Contrary to some reported statements, MHRA, as the responsible regulatory authority in the United Kingdom, made the decision to suspend Chiron's license after an internal meeting on October 4 and first informed the company and the FDA of this decision on October 5. At the same time, we informed other drug regulatory authorities via an intergovernmental rapid information alert."

Upon learning of the MHRA's suspension on October 5, 2004, FDA communicated with both Chiron and the MHRA. While Chiron indicated to FDA

that it believed it had satisfactorily addressed MHRA's inspectional findings and provided to FDA a copy of those findings and the company's response, MHRA expressed serious concerns about Chiron's vaccine stocks and the company's ability to assure the safety of the vaccine.

FDA Officials Dispatched to the U.K.

FDA dispatched a senior team of scientists, led by Dr. Jesse Goodman, the Director of FDA's CBER, to the U.K. on Wednesday, October 6, 2004, to gain further understanding of the MHRA's action. The team met with the MHRA on October 7, and met with Chiron on October 8.

FDA inspected Chiron's Liverpool manufacturing facility from October 10 through October 15, to evaluate the company's efforts to test for and assess the bacterial contamination detected in nine of the one hundred final vial lots of its influenza vaccine. FDA also evaluated Chiron's determination that the risk of bacterial contamination was confined to specific lots.

On October 15, 2004, upon completion of its inspection, FDA determined that it could not adequately assure that Chiron's vaccine met our safety standards. On October 15, we also provided Chiron with our inspectional observations (Form FDA 483) from our inspection and met with the company to discuss its compliance issues. FDA will continue to work with Chiron and the U.K. government to ensure that the company corrects the deficiencies in the Liverpool

plant so that it can eventually resume production of a safe and effective influenza vaccine. In the wake of the October 2004 inspection, FDA will work closely with MHRA and Chiron to assess any proposed corrective measures that the company submits in response to the October inspection and the company's findings of contamination in final lots. FDA will analyze Chiron's responses for their thoroughness, accuracy, and their adequacy. Ultimately, however, the agency's final determination regarding the effectiveness of Chiron's corrective measures will be based on a comprehensive inspection that we anticipate will occur once the company has notified the agency in February or March 2005 of the proposed corrective measure.

FDA's Response to the Flu Vaccine Shortage

Assuring the safety and effectiveness of vaccines is central to FDA's mission. Our goal is to assist the health care community as they work to provide protection to more Americans against the flu. To assist in these efforts, both Aventis Pasteur and MedImmune have indicated to FDA that they will provide additional doses of influenza vaccine. As a result, we have increased the available supply of licensed flu vaccine for the U.S. population to 61 million doses for this flu season, Aventis Pasteur will produce a total of 58 million doses of Fluzone and MedImmune has scaled up production to produce a total of 3 million doses of FluMist. FluMist is recommended for healthy individuals 5 to 49 years of age, and therefore, provides an option for those who would not receive

vaccine under CDC's priority guidelines as well as for certain categories within the CDC guidelines.

In addition to supplies of vaccine approved for use in the U.S., we have also identified about five million doses of influenza vaccine from foreign manufacturers that could potentially be available under investigational new drug applications (INDs). We have sent FDA inspectors to the manufacturing facilities of GlaxoSmithKline (GSK) in Germany and ID Biomedical in Canada to evaluate their manufacturing processes. These efforts could result in as much as 4 million doses from GSK and up to 1 million doses from ID Biomedical. Finally, in an effort to expand further the supply of vaccine to those with the greatest need, Secretary Thompson recently announced that military personnel will maximize the use of FluMist and Defense agencies will allow HHS to purchase 200,000 doses of injectable vaccine for which they had originally contracted so that we can make it available to the high-risk population in the U.S.

We have also been contacting manufacturers worldwide in an effort to identify increased supplies of antiviral medications. Antiviral medications are drugs that are approved to reduce symptoms and in some cases prevent onset of influenza if taken early after exposure has occurred. These drugs will help protect and treat for Americans during this flu season, and we are making progress in this area as well. There are enough antiviral medicines to treat influenza in 40 million Americans, if necessary.

To address the complications of those who experience the flu, Merck & Company plans to triple its production of pneumococcal polysaccharide vaccine from 6 million to between 17 and 18 million doses. Pneumococcal pneumonia is one of the most important and common serious complications of influenza, and the availability of this expanded supply during the current flu season will allow public health officials to lessen the possibility of this complication.

Preparations for Next Year

Aventis Pasteur believes they have the capability of producing the same or more doses of influenza vaccine for the 2005-06 flu season. In addition, MedImmune has indicated that it has the capability to produce 10 million doses of FluMist for the 2005-06 flu season and as much as 40 million doses by 2007.

We will continue to work with Chiron Corporation, in close collaboration with the UK regulatory authorities, to help Chiron address, as quickly as possible, the manufacturing problems they experienced during this year's production process. To this end, we have reached agreements with Chiron that allows for full sharing of information between the FDA and the MHRA as the company works to resolve the problems in Liverpool. In addition, FDA has also been encouraging foreign licensed manufacturers to apply for U.S. licensure, and is providing clear pathways to efficiently reach this goal.

Looking to the Future

Immediately upon coming to HHS, Secretary Thompson under the leadership of President Bush began transforming the flu marketplace by investing in new technologies, securing more vaccines and medicines, and preparing stronger response plans. The largest investments ever made by the federal government in protecting against the flu have been made under President Bush's leadership.

In keeping with these unprecedented investments, we must move science forward to help create more efficient ways to produce flu vaccine so we have greater flexibility to deal with shortages or unexpected problems. In each of the past two budgets, the Department has requested $100 million to shift vaccine development to new cell-culture technologies, as well as to provide for year-round availability of eggs for egg-based vaccine. We received $50 million in the FY04 budget for this activity and urge Congress to fully fund the $100 million request in FY05 budget.

To help manufacturers overcome challenges such as the vaccine development problems Chiron is experiencing, FDA has been investing its energy and resources in important initiatives such as the Current Good Manufacturing Practices for the 21st Century (known as the cGMP initiative).

Under the cGMP initiative, FDA is working with industry to encourage the use of advanced technologies as well as quality systems and risk-based approaches that build quality into the manufacturing process. FDA is also using the same

quality systems and risk-based approaches to modernize our manufacturing regulatory responsibilities. For example, we are providing advanced training for manufacturing investigators. This has led to greater inspection consistency and the ability to more readily identify manufacturing deficiencies. The cGMP initiative is also promoting better communication between manufacturers and the agency, which will enable manufacturers to anticipate and overcome production problems before they occur. Among the lessons we have learned from this year's events at Chiron is the need to enhance our international regulatory collaboration and harmonization efforts.

In the past year, we completed information sharing agreements with the European Medicines Agency, Health Canada, and SwissMedic, and most recently MHRA, to help assure that legal barriers do not inhibit critical communication between these agencies and FDA. FDA is undertaking an inventory of foreign manufacturing of U.S.-licensed products, such as flu vaccine, that are critical to public health, and will put into place information sharing agreements with other national regulatory authorities as needed. In addition, we recognize that public health needs and resources are increasingly global in nature and, in the hope that vaccines can be licensed in multiple regions of the world, FDA has been encouraging more internationally harmonized product development.

Recent events have highlighted how imperative it is that we support the U.S. and global vaccine manufacturing infrastructures and invest in more efficient, reliable and modern methods for producing influenza vaccine. With adequate supply and inoculation, influenza is manageable and we will be more likely to successfully face the challenge of future pandemics.

Once again, thank you for the opportunity to come here today and testify on this very important issue.

I would be happy to respond to any questions that members of the Committee may have for me.